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January 2, 2003

Re: IDE #G980067
Automated External Defibrillator (PAD-I)

Paul A. Williams, B.S.E.
Investigational Device Exemption Program
Office of Device Evaluation
Center of Devices and Radiological Health
IDE Document Mail Center (HFZ-401)
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

Dear Mr. Williams:

Enclosed in triplicate are the documents you requested for the demonstration of public disclosure to communities for the PAD Trial. These items are grouped by individual site, and include the original IRB submission and approval.

A preliminary summary of the material is also attached as a draft of a paper (including Tables), outlining the methods used by the sites to disclose their activities to the communities. This manuscript draft is a work in progress and is subject to revision.

Also attached are the most recent Data and Safety Monitoring Board minutes and the NHLBI summary of the most recent meeting, at which the Board recommended that the study be extended to September 30, 2003.

A copy of this material has also been sent to the Dockets Management Branch, as you requested.

Please let us know if you need any further material. We plan to submit the information used to disclose the results of the study to communities when it has been completed.

Sincerely,

H. Leon Greene, M.D.

955-0158 RPT 8

Public Access Defibrillation

CONFIDENTIAL DRAFT—Do Not Distribute

Conducting Cardiac Arrest Research With Exception from Informed Consent: The Public Access Defibrillation (PAD) Trial Experience

by

The PAD Investigators

Running Title: Exception from Informed Consent – the PAD Trial

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Abstract

Introduction: The Public Access Defibrillation (PAD) Trial is a prospective, multicenter, randomized clinical trial comparing survival of victims of out-of-hospital cardiac arrest when treated by volunteer, non-medical responders using standard cardiopulmonary resuscitation (CPR) and those using CPR plus an automated external defibrillator (AED). It is being conducted under the exception from informed consent regulations (21CFR50.24) at 24 cities in North America.

Methods: Using structured questionnaires, participating sites reported the activities required by their Institutional Review Board (IRB) to conduct the trial with an exception from informed consent.

Results: All trial sites received IRB approval, but an average of two revisions of the IRB application was required. The average time from submission to approval was 138 ± 121 days. The community consultation and public disclosure activities and their costs varied greatly from site to site.

Conclusion: Local activities and costs varied greatly in meeting the current regulations for conducting emergency research with exception from informed consent.

Key words: cardiopulmonary resuscitation (CPR)

automated external defibrillator (AED)

defibrillation

emergency medical services (EMS)

ventricular fibrillation (VF)

out-of-hospital cardiac arrest (OOH-CA)

exception from informed consent

community consultation

public disclosure

waiver of informed consent

Introduction

The ethical principles for human research are embodied in the Nuremburg Code {1, 2}, the Helsinki Declaration {3}, and in the United States are formalized in the Code of Federal Regulations (CFR) {4}. The primary principles of autonomy, beneficence, and justice are upheld through the rigorous implementation of informed consent. As stated in the Belmont Report, the ethical conduct of research requires that "...subjects, to the degree that they are able, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied." {5} No method of protecting the research subject's rights is equal to obtaining prospective consent from the informed individual.{6} Recently, the US Secretary of Health and Human Services reaffirmed that the American people expect clinical researchers will never compromise the safety of human subjects, and warned that if this confidence is violated both public funding and volunteer subjects would evaporate. {7}

Yet, it has long been recognized that research can be conducted ethically without informed consent. {8} The Declaration of Helsinki discussed conditions for both proxy and waiver of consent. {3} The emergency medical setting is one of those situations that require reconsideration of informed consent as a necessary precedent to the conduct of research. Individuals with a medical emergency may not have the capacity to provide informed consent due to physical, psychological or emotional duress. Yet, they are arguably the most in need of effective treatment. Healthcare providers have an ethical obligation to determine the most effective therapy through carefully conducted research, while protecting the rights of individual subjects. {8} Societal benefits (discovery of

more effective therapies for medical emergencies) must be balanced with individual rights (autonomy, beneficence and justice).

In 1993, a United States Food and Drug Administration (FDA) memorandum banning deferred consent effectively placed a moratorium on all research without prospective informed consent (except for research that involved minimal risk). {8} With input from emergency researchers, in 1996 the FDA and the Department of Health and Human Services (DHHS) published regulations (21 CFR 50.24) addressing the conduct of emergency research with exception from informed consent. {4, 9-10} Despite these regulations, there is a growing concern that little emergency research is being performed in the United States. {11} Some researchers believe the regulations are unnecessarily burdensome and that Institutional Review Boards (IRBs) may be uncertain about how to interpret them. {12} These concerns are heightened by recent incidents that have generated intense governmental and public scrutiny. {13}

The investigators of the Public Access Defibrillation Trial (PAD) accepted the challenge of conducting research under the new regulations. This paper focuses on IRB process issues, costs, the activities conducted to achieve community consultation and public disclosure, and the major additional protections required for research conducted under the emergency exception.

Methods

The PAD Trial is an international, multi-center, randomized controlled study of two strategies for the initial care of patients with out-of-hospital sudden cardiac arrest (OOH-CA).{11} Both strategies include implementation of an alerting system to activate on-site, non-medical, lay volunteer responders and the local emergency medical services (EMS) immediately when a subject collapses. The control strategy consists of training responders to perform basic cardiopulmonary resuscitation (CPR), while the intervention strategy added training and on-site deployment of AEDs. Investigators at 24 sites across the United States and Canada enlisted over 1,000 study units (locations such as shopping malls, gated communities, and sports venues) with a population of >250 persons over age 50 or a documented history of at least one cardiac arrest annually. The primary outcome measure is the number of survivors of OOH-CA.

This trial involves two groups of subjects. The first group consists of the volunteer responders at study units. These volunteers were all trained in CPR and some in use of the AED. Demographic and performance data was collected. Prospective, written informed consent was obtained from these subjects.

The second group of subjects is persons who suffer a suspected OOH-CA at study locations. These subjects receive an intervention based upon unit randomization. Although both interventions represent medically accepted therapies and FDA-approved use of the AED, informed consent would typically be required since they are applied in randomized fashion under the auspices of research. The study also involves the collection of identifiable process and outcome data from the time of the incident through

the end of the study (3-24 months after hospital discharge). However, subjects who meet the eligibility criteria (unresponsiveness and suspected OOH-CA) are incapable of providing consent. The interventions being evaluated must be applied immediately to be effective, prohibiting obtaining consent from next of kin.

The PAD Trial investigators identified two potential mechanisms for addressing the issue of informed consent from this second group of subjects. The study could be considered "minimal risk;" requiring IRB approval but obviating the need for individual patient consent. The alternative is to follow the regulations for exception from informed consent for emergency research.

Discussions were held among investigators, the CTC, the FDA, and the primary sponsors (the National Heart, Lung, and Blood Institute [NHLBI] and the American Heart Association [AHA]). Specifically considered was whether "minimal risk" refers to the probability and magnitude of harm normally encountered in patients with the respective disease or condition (i.e., a relative standard) or to that encountered in the daily life of a member of the general public (i.e., an absolute standard). Cardiac arrest is clearly a high-risk condition, with a likelihood of death approaching 97% in many cities {12-13}, but the risk level attributed to a research trial usually refers to the *incremental risk of the study interventions themselves*. CPR performed by layperson bystanders is a currently accepted treatment for OOH-CA and the use of the AED fell within FDA approved indications. Thus, the trial presented no significant *additional* risk than what would typically be encountered by victims of OOH-CA.

The FDA insisted, and most parties to the discussion agreed, that the absolute standard should apply. Furthermore, for the results to be applied to any subsequent

attempt for reclassification of AEDs as non-prescription devices, the study would have to be done with an Investigational Device Exemption (IDE). Based on the FDA's position, discussion with the IRB at the University of Washington, and the majority opinion, the decision was made to proceed under the exception for emergency research regulations (21CFR50.24). (Table 1)

The CTC obtained approval through the University of Washington IRB for the collection and analysis of data. The CTC and IRB Subcommittee of the PAD Trial's Steering Committee provided guidance on the regulations and sample informed consent documents, but each site was responsible for preparing its own IRB submission.

Each site was required to submit documentation of local IRB approval to the CTC. Site investigators reported the time required for IRB approval, the number of protocol revisions, types and number of community consultation (CC)/public disclosure (PD) activities, the number of positive, negative and neutral comments generated by community consultation and public disclosure, and the costs associated with CC/PD activities. Costs were defined as "those for which a statement, bill or receipt was or could have been produced" and specifically excluded "the cost of personnel time." Investigators were also surveyed about their perceptions of the difficulty of obtaining IRB approval and the number of major and minor protocol revisions that were required. The authors contacted investigators by e-mail and/or phone to clarify any missing or ambiguous responses.

Results

All twenty-four sites were successful in gaining IRB approval and provided documentation to the CTC. All sites also completed the surveys on CC/PD activities and their perceptions of the IRB process. The three Canadian sites are excluded from the survey results.

The average time from submission to approval by the primary IRB was 138 $\pm$ 121 days (range: 1 to 404; median: 108; IQR: 43-196). Fourteen of the sites had to submit the protocol to multiple IRBs. Of the 24 sites, 101 different IRBs reviewed and approved the trial.

The primary IRBs requested an average of 2 revisions (range 0 to 7), with a mean of 1 major revision (range 0 to 6) as classified by the local investigator. Specific revisions varied greatly but major revisions most frequently involved the CC/PD process. They included extension of the process timeline, formation of a community advisory board and specific instruction on the content and type of advertising. In a few instances, investigators successfully convinced the IRB to rescind a requested revision. The most notable example of this was an initial request by an IRB to obtain prospective consent from all occupants of gated communities and apartment complexes.

Investigators used a variety of mechanisms to assure the IRB they would be in compliance with the requirements for exception from informed consent. No single mechanism was used by all the sites. The most common were including the national PAD protocol (n=20), an appendix detailing the compliance plan (n=19), or personally meeting with the IRB chair (n=18) (Table 2).

The types and numbers of activities undertaken at each site to fulfill the community consultation and public disclosure requirements were quite diverse. (Tables 3-6) Study-wide, the CC/PD process resulted in: 1,030 meetings, attended by at least 8,169 individuals; 475 press releases; distribution of 9,270 letters, brochures, newsletters, or emails; 231 radio, television, or print advertisements; posting of 459 notices; 286 feature news stories; and 75 radio or television appearances.

A total of 1,502 comments were received, of which 96% were reported as "positive." Only 14 (1%) negative comments were reported. The community consultation meetings generated more than two-thirds of the comments. (Table 7)

The reported direct costs for the CC/PD activities totaled $31,560, or a mean cost of $1,315 per site. Nine sites incurred no direct costs associated with their CC/PD activities, while the maximum cost reported by any single site was $13,233. (Table 8)

Ten (42%) of the sites found the IRB process significantly harder than usual; 6 (25%) found the process a little harder than usual; 7 (29%) found the process neither harder nor easier than usual, and 1 (4%) found the process a little easier than usual. Meeting with the IRB administrator/chair or full IRB did not significantly affect the time required for IRB approval, the number of revisions required, nor the number of major revisions required. Those sites that met with the IRB administrator or chair were more likely to rate the IRB process as "harder than usual," when compared to those sites that did not meet with the IRB administrator or chair (Wilcoxon Rank Sum Test, $p = .003$).

Discussion

The PAD Trial, involving over 1,000 locations in 24 North American cities, is the largest study to utilize the regulations allowing exception from informed consent for emergency research. Researchers have been concerned that it would be extremely difficult to obtain IRB approval under the new federal regulations, both due to the extensive criteria and the lack of definition of the requirements. {10} [Valenzuela and Copass] [Pearson K. Anesthesiology. 89(5):Nov 1998:1047-49] This trial provides some reassurance that conducting such research is tenable and that most IRBs have taken a reasonable approach to the regulations. The process at the site level likely was facilitated by extensive review at the national level, by the NHLBI, AHA, a panel of resuscitation research experts, and ultimately by the University of Washington. Each investigator had to design and implement site-specific CC/PD. Ultimately, all of the sites were able to fulfill the requirements of their respective IRBs, and all received approval for the study.

IRBs requested one major and one minor revision on average at each study site, but some sites required multiple major revisions. This could reflect that IRBs and researchers have little experience and inadequate guidance for implementing studies using exception from informed consent. The lack of clarity and specificity in the regulations resulted in a situation in which even experienced researchers were unable to anticipate the requirements of their respective IRBs, and in which the IRBs themselves had difficulty interpreting and applying those regulations. This led to delays for approval and increased work for both the investigators and for the IRBs.

The CC/PD activities required significant effort at modest cost. There were more than 2,500 distinct CC/PD activities at a total cost of $31,560. This figure includes only documented expenses, not "in-kind" services and goods, and does not reflect investigator or staff time for presentations, meetings, media appearances and preparation of print materials, which was felt to be considerable (but not quantified) by investigators.

The variability in the amount of effort and types of activities required among the 24 sites makes it difficult to predict or estimate the resources that would be necessary for a future study of similar design. At sites where only discrete, isolated units were being used (e.g., gated residential communities) the process of CC/PD was much simpler than for sites recruiting units that had general public access (e.g., shopping malls). CC/PD could be performed at discrete units by holding meetings of the residents. For the sites with public access units, citywide consultation and disclosure were typically necessary, requiring mass media techniques.

The process generated 1,500 comments, an average of less than one comment per activity; only one percent of those comments were negative. Demonstrating the community's acceptance of the study protocol to the IRB is important as identifying and addressing problems or concerns through the CC/PD process. Whether the relatively small total number of comments and the fact that the overwhelming majority was positive accurately demonstrate the community's acceptance cannot be determined from our data.

The PAD experience has been distinctly different from that of Kremers et al. {14}, who undertook a single-institution study of vest CPR that required exception from informed consent. Despite having to work with only one hospital, one IRB, and one community, the investigators reported significant difficulty in fulfilling the requirements

to the satisfaction of the IRB. Interestingly, patients and community members were not the sources of concern. Hospital administrators were concerned about liability, and IRB members were uncomfortable with the responsibility of interpreting and applying the FDA regulations.

Another study {15} conducted in 18 hospitals, and enrolling 112 patients over a one-year period, may have had less difficulty in obtaining IRB approval because it provided for obtaining informed consent prior to enrollment when feasible. In actuality, prospective consent occurred in only 6 of the 98 patients who were randomized, suggesting that obtaining informed consent in emergency situations, even non-arrest situations, is not feasible in most instances.

Baren's et al. {16} approach to CC is to describe the study to appropriate emergency department patients and ask if they would agree to participate. They suggest that such an exercise would enable researchers to determine the acceptability of a research protocol among likely subjects, and to identify and address any issues or concerns raised during that process.

Passamini and Weisfeldt outlined a number of actions to facilitate research conducted with the emergency exception. {7} They emphasize the importance of resuscitation research, the need for additional education of investigators, IRBs and the public, and the value of specific criteria for allowing the exception They suggest that a federal advisory group and a strong, experienced national IRB would greatly enhance the quality and quantity of emergency research in the United States.

Exception from informed consent should be carefully distinguished from obtaining a waiver of informed consent under 45 CFR 46.116d, which is applicable to

research with minimal risk. To avoid potential confusion and mitigate the need to repeatedly reference the intended regulation, we propose using the term "exception from informed consent" to refer to the emergency exemption under DHHS/FDA title 21 CFR part 50.24 and the term "waiver" for that meeting the minimal risk criteria.

This study has limitations. The subjective responses to the questionnaires may reflect biased opinions of the investigators. The report of costs for achieving IRB approval may be underestimated because the personnel expenses (and time spent on community consultation and public notification activities) were not tracked prospectively. For these reasons, estimates of these costs were excluded from the analysis. Time spent by personnel on community consultation and public notification activities likely represent the majority of the expenses for meeting the exception for informed consent under emergency circumstances..

The PAD Trial demonstrates that a large multi-center trial enrolling cardiac arrest patients under the rules for exception from informed consent for emergency research is possible. This effort, which required approval by multiple IRBs in diverse communities, provides insight into the understanding of the CC/PD requirements. The activities associated with fulfilling the requirements of those regulations are substantial and vary from site to site. There was little feedback from the public and the comments were overwhelmingly positive.

Investigators, institutions, and sponsors undertaking exception from informed consent research should allocate sufficient time and resources for the process, work proactively with their IRBs, and have realistic expectations of the level of community input they will receive.

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Table 1—Summary of the Exception from Informed Consent Requirements for Emergency Research (21CFR50.24)

Justifications

1) The research involves a medical condition or situation in which:
   a) Human subjects are in a life-threatening situation.
   b) Available treatments are unproven or unsatisfactory.
   c) Evidence is necessary to determine the safety and effectiveness of particular interventions.
2) Obtaining informed consent is not feasible because:
   a) The subject is not able to give consent due to his or her medical condition;
   b) The intervention must be administered before obtaining consent from legal representative is feasible.
   c) There is no reasonable way to identify eligible subjects prospectively.
3) Participation holds out the prospect of direct benefit to the subjects because:
   a) Subjects face a life-threatening situation which requires intervention.
   b) Preliminary investigations, including animal studies, and related evidence suggest that this intervention may provide a direct benefit to the individual subject.
   c) The risks are reasonable.
4) The clinical investigation could not practicably be carried out without the waiver.

Obligations of the Investigator

5) The proposed study protocol defines the length of the potential therapeutic window, and the investigator:
   a) Commits to attempt to contact and, if feasible, to obtain consent from a legally authorized representative for each subject within that window of time; and
   b) If a legal representative is not available, commits to attempt to contact within that window some other family member and ask if that family member objects to the subject's inclusion; and
   c) Will summarize the efforts made to contact legal representatives and family members and make this information available to the IRB at the time of continuing review.
6) Consultation with representatives of the communities in which the research will be conducted.
7) Public disclosure to the communities where the research is conducted:
   a) Prior to initiation of the trial regarding the study plans, risks and benefits;
   b) After completion, of the results and subject demographics.
8) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation.
9) Perform the study under a separate investigational new drug application (IND) or investigational device exemption (IDE) from the Food and Drug Administration, even if an IND or IDE already exists.

Obligations of the IRB

10) The IRB has reviewed and approved procedures and documents for:
   a) Use in situations when obtaining informed consent is feasible;
   b) Use when providing an opportunity for a family member to object is feasible.
11) The IRB is responsible for assuring that procedures are in place to:
   a) Inform each subject, or a legally authorized representative or family member (if the subject is incapacitated) of his or her inclusion in the study and details of the study;
   b) Inform each subject or representative that he or she may discontinue participation in the trial;
   c) Inform subjects who become competent after initial notification to representatives of incompetent subjects;
   d) Inform a legally authorized representative or family member of subjects who die prior to notification about the trial.
12) If an IRB determines that it cannot approve a proposed study because it does not meet the criteria for justifying the need for a waiver or for other ethical concerns, the IRB must provide these findings promptly to the investigator and sponsor in writing.
13) The IRB must retain the determinations and documentation required by the above regulations for three years.

Obligation of the Sponsor

14) If an IRB denies approval of a protocol per item 12, the sponsor of the investigation must promptly disclose this information to the FDA, the clinical investigators and other IRBs that have been or are asked to review the same or a substantially equivalent trial.

Table 2: Mechanisms by which sites assurred their IRB that investigators would comply with, the requirements for waiver of informed consent.

Activity	Sites (N)
Standard IRB application forms	21
A separate narrative summary of the project	17
Specific forms required by individual IRB exclusively for waiver of consent	5
Appendices to the IRB application (other than the national PAD protocol)	19
National PAD protocol (as an appendix to the IRB application)	20
Meeting / discussion with the IRB administrator / chair	18
Presentation to / meeting with the entire IRB board	11
Other	4

Table 3: Community consultation and public disclosure activities undertaken by the sites - meetings.

Activity	Number of Sites - CC	Number of Sites - PD	Total Activities
With survivors of cardiac arrest	7	2	17
With family members of non-survivors of cardiac arrest	5	1	12
Open to the community at large	16	10	60
At community events (i.e., street fairs, festivals)	4	3	20
With panels of community representatives	11	3	35
With local clergy	3	1	10
With leaders of local ethnic groups	4	2	15
With groups of invited participants	7	5	21
With community advisory boards	10	6	41
With each "unit's" community	10	8	152
With the boards of directors of potential "units"	11	4	148
At local government meetings / forums	7	5	54
At state government meetings / forums	4	1	25
With EMS personnel	18	15	191
With hospital staff	9	7	76
With local physicians (separate from hospital staff)	8	3	57
At "grand rounds" or other educational conferences	7	4	16
With local or state medical boards	4	2	12
Other, unspecified	4	1	68

Table 4: Community consultation and public disclosure activities undertaken by the sites - radio/television.

Activity	Number of Sites - CC	Number of Sites – PD	Total Activities
Paid advertising on television	0	1	25
Free advertising on radio	6	3	25
Free advertising on television	4	2	35
Feature news stories on television	13	2	56
Feature news stories on radio	9	9	52
Press releases to radio stations	11	6	35
Press releases to television stations	12	7	38
Appearances on local radio shows	8	8	32
Appearances on local radio call-in / talk shows	2	1	7
Appearances on local television shows	7	5	36

Table 5: Community consultation and public disclosure activities undertaken by the sites - print media.

Activity	Number of Sites - CC	Number of Sites – PD	Total Activities
Paid advertising in general distribution newspapers	7	3	29
Free advertising in general distribution newspapers	7	3	52
Press releases to general distribution newspapers	13	11	240
Feature stories in general distribution newspapers	14	7	69
Paid advertising in community-specific newspapers	3	2	20
Free advertising in community-specific newspapers	4	2	25
Press releases to community-specific newspapers	9	5	162
Feature stories in community-specific newspapers	4	5	25
Advertising in local newsletters	3	1	20
Feature stories in local newsletters	7	5	84
Distribution of a PAD specific newsletter	4	4	47
Distribution of flyers / brochures	13	9	7910
Distribution of letters to the community at-large	2	5	120
Distribution of letters to each "unit's" community	9	5	588
Distribution of letters to community leaders	10	3	468
Posting of notices throughout the community	3	2	59
Posting of notices at each potential "unit"	6	6	374
Other, unspecified	0	1	1

Table 6: Community consultation and public disclosure activities undertaken by the sites - telephone/electronic communication.

Activity	Number of Sites - CC	Number of Sites – PD	Total Activities
Establishing a telephone "hot line" to receive comments	11	8	19
Telephone survey of members of each "unit's" community	1	0	1
E-mail announcement to the community at-large	1	0	2
E-mail announcements to each "unit's" community	2	1	106
E-mail announcements to community leaders	2	1	29
Advertising / postings on existing web-pages	6	4	26
Development of a local PAD specific web site	6	3	9
Hosting web-meetings / chat rooms	1	0	1
Other, unspecified	1	1	51

Table 7: Comments received during community consultation / public disclosure.

Source	Positive	Negative	Neutral	Total
CC Meetings	1056	9	14	1079
CC Radio/TV	17	0	0	17
CC Print Media	171	2	5	178
CC Telephone/Electronic	12	0	0	12
All CC Activities	*1256*	*11*	*19*	*1286*
PD Meetings	25	2	24	51
PD Radio/TV	34	0	0	34
PD Print Media	66	1	4	71
PD Telephone/Electronic	60	0	0	60
All PD Activities	*185*	*3*	*28*	*216*
All CC and PD Activities	**1441 (96%)**	**14 (1%)**	**47 (3%)**	**1502**

Table 8: Costs associated with community consultation / public disclosure activities (US Dollars).

Source	Minimum	Maximum	Mean	Total
CC Meetings	0	8,755	631	15,156
CC Radio/TV	0	150	9	210
CC Print Media	0	2,460	240	5,766
CC Telephone/Electronic	0	1,200	50	1,200
All CC Activities	*0*	*8,755*	*930*	*22,332*
PD Meetings	0	100	8	200
PD Radio/TV	0	2,000	90	2,150
PD Print Media	0	2,478	237	5,678
PD Telephone/Electronic	0	1200	50	1,200
All PD Activities	*0*	*4,478*	*385*	*9,228*
All CC and PD Activities	**0**	**13,233**	**1,315**	**31,560**

PAD DSMB Meeting
June 13, 2002
9:00 a.m. – 3:00 p.m. EST
Washington, D.C.

PAD DSMB Minutes

Attending: Dr. Lambrew, DSMB Chair; Dr. Braslow, DSMB; Dr. Feldman, DSMB; Dr. Goff, DSMB; Mr. Gonzalas, DSMB; Dr. McCullough, DSMB; Dr. Ornato, PAD Executive and Steering Committee Chairs; Dr. Salive, NHLBI Project Officer; Dr. Simons-Morton, NHLBI; Dr. Proschan, NHLBI Statistician; Dr. Rosenberg, NHLBI, DSMB Executive Secretary; Dr. Greene, PAD CTC; Dr. McBurnie, PAD CTC;

Project Office Report

The Project Officer reconfirmed the importance of the PAD Trial to the Institute. NHLBI is also preparing to fund a new Trial on home defibrillation. Some of the PAD DSMB members may be approached to serve on the DSMB for that study also. It was also noted that, because of the potential for perceived conflicts of interest, the members of the Project Office team for a particular study may not serve as the Executive Secretary (ES) for that study's DSMB. Denise Simons-Morton served as ES for this meeting. Yves Rosenberg will fulfill this role in the future.

Overview

Dr. Ornato began by commenting on the uniqueness of the data being collected for the PAD study. He emphasized the importance and relevance of the data to current public health issues. In particular, the waiver or exception to informed consent issue has been a topic of considerable interest lately. Recently, the National Association of Emergency Physicians sponsored a conference on that topic. In addition, Bill HR 4697 - also known as the Human Subjects Research Protections Act of 2002 - was discussed, the intent of which appears to prohibit federally funded research in at least some situations where the an IRB has approved an exception to informed consent. The American Heart Association (AHA) may oppose this legislation. Also mentioned was the passage of the Rural AED Act which makes millions of dollars available for AED placement in rural communities, but which should not directly adversely affect the PAD Trial. The Board noted the New England Journal of Medicine's recent decision allowing authors to have a conflict of interest of up to $40,000.

Next, the statement by AHA regarding implementation of AED programs in fitness centers was discussed (Automated External Defibrillators in Health/Fitness Facilities: Supplement to the AHA/ACSM Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities, written by Balady GJ, et al. *Circulation* 2002 105: 1147 – 1150). The AHA has essentially recommended that AED programs be implemented in all fitness centers. The statement contained weak, indirect evidence in support of its recommendations. However, there is considerable potential for influencing public perception and negatively impacting the PAD study's efforts to obtain objective data.

The Board reviewed the statement and opined that the guidelines went beyond the evidence provided. Several communications have taken place between PAD

representatives and AHA personnel concerning this issue and the Board suggested that NHLBI also comment to AHA. In addition, the Board requested that a generic statement be developed summarizing what is known regarding the effectiveness of PAD programs in fitness facilities based on currently available data. The statement should also summarize the ongoing work in progress of PAD and other studies. The DSMB would like to review the statement, which should be made available to sites, study units and the press, particularly when events are covered.

Recruitment and Training

Ninety-five percent of trial on-line units have received initial training. The remaining units tend to be those that have chosen to "drop out" of the study or have, for some reason or other, indicated a reluctance to schedule training. Of units reaching the 3 month initial retraining window, 66% and 72% of CPR-only and CPR+AED units had been retrained, respectively. Average time to retraining for these units was about 6.5 months. For units reaching their randomized "subsequent" retraining window, approximately 50% had been retrained again. The training burden has been a major challenge for the sites, in large part because the number of volunteers is approximately twice what was originally anticipated, and there is some attrition after the initial training. Furthermore, the CTC has instructed sites that establishing episode data collection procedure should be the top priority.

There was some discussion regarding volunteers who did not meet proficiency criteria during retraining. Generally volunteers are retrained until they do meet the criteria, however, in rare cases where volunteers do not meet the criteria, they are still allowed to participate in the study. The Board considered whether such a volunteer would be a safety risk, however, they concluded that allowing the volunteer to continue participation was no worse than the expected response in the absence of a response system. It was suggested that such volunteers be encouraged to yield to those with stronger skills, if present. Some additional analyses were suggested by the Board, including determining the number of volunteers failing to retrain to proficiency, analyzing success/failure of resuscitation attempts by retraining times, and computing the average number of months to retraining at the volunteer level (versus the unit level).

Data QC

Completeness of submitted baseline, training and AED forms is >95% for the majority of sites. The percentages are lower for the episode and hospitalization forms as there can be substantial lag time to completion of the forms due to the fact that the data come from a variety of sources. Two sites, Washington D.C. and Richmond, were missing 100% of the April quarterly volunteer and AED logs. Eleven sites had incomplete EMS packets. No surviving patients have refused to participate in follow-up, although, occasionally the first one or two interviews were missed due to difficulty locating patients and/or obtaining consent.

Adverse Situations

The Board identified no serious adverse situations. However, there was considerable discussion regarding a Vancouver episode in which the Board felt that defibrillation had

not been delivered in a timely manner. During this episode, upon being opened to perform a rescue attempt, a Survivlink AED prompted the volunteer to "press flashing button to resume rescue." This prompt occurred because the device initially detected impedance consistent with that of a human body. The volunteer, confused because the device failed to shock the patient when he pushed the button, assumed that the device was malfunctioning. However, the device proceeded to analyze the rhythm, detected a shockable rhythm and advised a shock. The Vancouver PI and Coordinator had expressed concern regarding this episode and a call between the study personnel and the manufacturer has been scheduled to discuss the issue. Two options were under consideration at the time: The first option was for the CTC to send a memo to all Survivalink sites, re-emphasizing the protocol and instructing them to remind volunteers in AED units of the importance of following the device prompts and the importance of performing the routine maintenance checks on the devices. Ongoing retraining of volunteers could also include instructions regarding the potential for similar types of episodes. The second option would be to disable the automatic impedance check performed by the device.

There was consideration of whether the Board's discussion of this episode constituted a "sentinel event" and what level, if any, of additional FDA interaction was necessary (the incident had already been included in a recently submitted annual report to the FDA). The Board concluded that the problem was one of efficacy, rather than safety, and that discussion among the Investigators, CTC and manufacturer should proceed without additional consultation with the FDA at this point. The Board requested that they be updated regarding these discussions and that they be notified immediately of any similar occurrences. In addition, they requested that a memo regarding this potential occurrence with Survivalink AEDs be developed and sent to the sites and that IRBs be notified that the memo had been sent at the request of the DSMB. They also requested that an addendum to the NHLBI DSMB summary to the sites be included for the Survivalink sites, summarizing the episode and the plan of action.

The minutes from the previous meeting were approved and the Open Session ended.

Closed Session

Episode definitions and the episode adjudication process were reviewed. Two sets of episode data were reported: one included all data collected from the units' Baseline on-line date and second was the subset containing data collected since the Final on-line date. Approximatey 46% of the planned Unit Exposure Months (UEMs) had been accrued for on-line data, with slightly more than 100% of planned UEMs expected by the March 1, 2003 termination date. Episode and cardiac arrest rates were reviewed by site and by treatment arm. A breakdown of episode classification was also given, as were selected demographics and other episode characteristics. No problems were evident concerning episodes involving DNAR patients. Also, of the reported delays to 911 calls, none appeared to be related to the study. There were one or two situations where CPR may have been delayed due to volunteer confusion because the victim had agonal breathing.

Interim Analysis: The Board reviewed the interim analysis, which included survivors verified as of May 14, 2002. The observed cardiac arrest rate is substantially lower than expected (~0.2 versus 1.0 per 15 UEM), and although the overall survival rate is greater than originally estimated, the power at the observed rates appears to be substantially lower than planned to detect a 2-fold difference in survival. At the current rates, as of March 1, 2003, approximately half of the expected survivors will be accrued, resulting in approximately 50% power to detect a 2-fold difference. There is roughly 80% power to detect a 2.5-fold difference, however, it was felt that it might be unreasonable to require that large an effect.

Graphs were presented illustrating the improvement in episode ascertainment and collection since the April Steering Committee Meeting.

Executive Session

The Board discussed the overall status of the trial and the various issues that arose during the open and closed sessions. They commended the Coordinating Center for producing an outstanding report.

The DSMB unanimously recommended that the trial continue and made the following recommendations:

AED problem: The DSMB discussed the case in which a Survivalink AED provided instructions resulting from a built-in self-test procedure, which was inconsistent with the situation (instructions were "resume rescue", but rescue had not been started). As a result, the volunteer failed to follow the AED's instructions. The patient did receive the current recommended standard of care (CPR and EMS treatment). The patient died from his cardiac arrest. Several other instances during routine checks of the same brand of device resulted in the same instructions by the device.

After considerable discussion, the Board considered this to be an efficacy rather than a safety issue. They recommended the following:

- this problem be reported to the concerned sites' IRBs in an addendum to the usual report they receive following each DSMB meeting
- a memorandum be sent to the concerned sites with detailed instructions to follow if such a problem were to occur again
- these DSMB minutes be sent to the FDA as an addendum to the usual annual report
- monitoring these types of cases continue, and the DSMB chair be notified immediately if other such events occur.

Event rate: The cardiac arrest event rate is less than projected at the beginning of the trial. Because of the small number of events, the confidence intervals for the event rates in the two groups are wide. As a result, the power of the study is difficult to calculate with assurance. The DSMB expressed concerned about the final power the trial might have to detect the expected treatment difference. In addition, concern was raised regarding the completeness of reporting of cardiac arrests by many of the sites. However,

they also noted that the trial may have other critical data with important health policy implications. They made the following recommendations:

- all sites be encouraged to continue follow-up through March 2003, even if that implies that some units would go beyond their scheduled 15 months participation
- efforts be made to improve the completeness of case reporting
- a DSMB conference call should occur in November to review the overall cardiac arrest rates (both groups combined) and revised power calculations. (Interim analysis by arm will not be conducted at that time).

National AED recommendations: The DSMB expressed concern that the AHA/ACSM recommendation for fitness facilities to provide AEDs was not evidence-based. This AHA/ACSM statement could have a potential negative impact on the future of the study, as it could result in "contamination" of control sites, and so should be addressed.

The DSMB recommended that the investigators and the NHLBI work with the AHA and ACSM on a joint statement on the evidence for public access defibrillation and the continuing importance of the research question.

Additional Data Analyses: Additional data analyses regarding training and volunteer dropout was suggested, including:

- data on time to retraining at the volunteer level, not just the site level, that would include the average and range as well as percent retrained by a specified time (e.g., 6 months)
- data on volunteer dropout rates over time (perhaps similar to a survival analysis).

Next DSMB meeting: Wednesday, November 13, 2002, 10:00 a.m. (Pacific) was set for the next DSMB conference call. The final DSMB meeting was tentatively scheduled for Tuesday, May 20, 2003.

The meeting ended at 3:20 p.m.

Costas T. Lambrew, M.D.
Chair

Denise Simons-Morton, M.D., Ph.D.
Acting Executive Secretary

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, MD 20892

MEMORANDUM

DATE: July 1, 2002
FROM: PAD Project Officer
SUBJECT: Report of the June 13, 2002, PAD DSMB meeting
TO: PAD Site Investigators

On June 11, 1999, "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-Center Clinical Trials" was published in the NIH Guide for Grants and Contracts. The purpose of the Guidance is to improve communications among Data Safety Monitoring Boards (DSMB), Principal Investigators, and Institutional Review Boards (IRBs). The Guidance requires all multi-site clinical trials with a DSMB to forward Summary Reports of Adverse Events to each IRB associated with the trial. Each Summary Report will include the following information:

- A statement that a DSMB review of data and outcomes across all centers took place on a given date;
- A summary of the DSMB review of the cumulative adverse events reported from all participating sites without specific disclosure by treatment arm, unless safety considerations require such disclosure, or a statement indicating no adverse events were reported from the participating sites, and
- The DSMB's conclusion with respect to progress or need for modification of the protocol.

The Summary Reports are in addition to all other adverse event reporting procedures required by the NHLBI, the trial protocol, the Statement of Work, the FDA, your organization, and your local IRB. The Summary Reports will be distributed to each Principal Investigator by the Coordinating Center within 30 days after each DSMB meeting. Principal Investigators are required to forward the Summary Reports to their local IRBs. Adverse events are defined in the PAD (Public Access Defibrillation) trial protocol and Manual of Operations.

A DSMB was established for the PAD Trial to monitor data and oversee patient safety. The DSMB is composed of one cardiologist, one internist, one paramedic, one statistician, and one ethicist appointed by the Director, NHLBI. The Study Chair, the Director and senior staff of the Clinical Trial Center, and representatives from the NHLBI participate as non-voting members. The DSMB procedures are identified in the trial protocol. The DSMB is scheduled to convene one-two times per year.

On June 13, 2002, the PAD Data and Safety Monitoring Board met to review interim results for the study. The DMSB reviewed enrollment, data submission, baseline comparisons, follow-up data, adverse events, and primary endpoints from all sites. In order to comply with the NIH Directive cited above, the following is reported. No serious adverse events have been reported from the participating sites. A review of recent literature relevant to the research took place. If a particular IRB requires further information they should contact the Clinical Trial Center directly. No aspect of the safety profile requires any change in the PAD trial. The DSMB concluded that the study should continue precisely as outlined in the protocol. They suggested no changes in treatment or follow-up procedures.

Marcel E. Salive, MD, MPH
Prevention Scientific Research Group, Division of Epidemiology and Clinical Applications
National Heart, Lung, and Blood Institute

ADDENDUM:

The DSMB discussed a case in which a Survivalink brand AED provided instructions resulting from a built-in self-test procedure, which were inconsistent with the situation (instructions were "resume rescue", but rescue had not been started). As a result, the volunteer did not follow the AED's instructions. The patient did receive the current recommended standard of care (CPR and EMS treatment). The patient died from his cardiac arrest. Several other instances during routine checks of the same brand of device resulted in the same instructions. The Board viewed this as an efficacy issue, and recommended that the site investigators and IRBs be notified of the problem with this particular AED device along with remedies to be implemented. The planned remedy is, initially, a training reminder to be sent to all relevant AED units and volunteers instructing that:

> On a rare occasion when opening the AED the voice prompt will state, "push flashing button to resume rescue" instead of the typical "place electrodes." If a prompt other than "place electrodes" is heard the volunteer should place the electrodes and follow the directions given by the AED.

In addition, the PAD Coordinating Center is working with Cardiac Sciences to implement a change in the AED voice prompt to eliminate this possible source of confusion.

Public Access Defibrillation (PAD) DSMB Conference Call
November 13, 2002

Attending: Dr. Lambrew (DSMB Chair); Dr. Feldman, DSMB; Dr. Goff, Mr. Gonzalas, DSMB: Dr. McCullogh, DSMB; Dr. Ornato, PAD Executive and Steering Committee Chairs; Dr. Salive, NHLBI Project Officer; Ms. Schron, NHLBI Deputy Project Officer; Dr. Proschan, NHLBI Statistician; Dr. Rosenberg, NHLBI/DSMB Executive Secretary; Ms. O'Neil, NHLBI Contracting Officer; Dr. Domanski, NHLBI; Dr. Hallstrom, CTC; Dr. Greene, CTC; Dr. McBurnie, CTC; Ms. Powell, CTC, Ms Van Ottingham, CTC.

Regrets: Dr. Braslow, DSMB.

Open Session
After roll call Dr. Lambrew welcomed the group and reported that there were no reports of serious adverse events since the last meeting.

The NHLBI indicated that the PAD Trial was important to the Institute and that it is part of NHLBI's overall strategy with regard to research on automated external defibrillators (AEDs). The FDA has recently approved an AED intended specifically for home use and the Institute has just funded the Home AED Trial (HAT), which will evaluate the effectiveness of AEDs in the homes of patients with a high risk clinical profile for cardiac arrest. In addition, DHHS released approximately $12 million in funding for rural AED programs.

It was noted that the original (unconditional) power planned for the PAD study was 78%, which is unusually low to begin a trial. Studies are usually planned to have 90% power for the specified alternative. The actual power is substantially less due to the lower than expected event rates. By extending the study to September 30, 2003, an acceptable unconditional power level will be achieved. Additional NHLBI funds will not be requested for the extension.

The Steering Committee Chair reported that the October 21-22, 2002, PAD Steering Committee Meeting had been productive and that the Committee recognized the importance of achieving a definitive answer with regard to the effectiveness of AEDs when used by lay persons in public settings.

The CTC reported on actions taken with regard to the Vancouver incident where a volunteer was confused by an AED prompt. The manufacturer has changed the prompt and the change has been distributed to the relevant sites that are currently updating their AEDs. In addition, an addendum to the IRB report was sent to affected sites. A copy of the minutes of the previous DSMB was sent as an addendum to the annual FDA report and an Operations Memo was distributed to the sites. Finally, flyers reviewing proper procedures for this device were developed for sites to distribute to the units.

Next, the status of volunteer training and retraining was summarized. Approximately 19,000 volunteers have been retrained with roughly 15,000 still active. About 27% of active volunteers had received their first retraining within the specified window of 3-6 months while 50% were due for retraining but had not yet been retrained. For the second retraining (randomized to 3-month intervals) about 15% had been retrained within the window ($\pm$ two week of target date), 30% were due but not retrained and 30% were not yet due. There were no apparent differences between the CPR and CPR+AED groups. The percent of volunteers performing adequate CPR skills declined by about 2% per month while the percent of volunteers performing adequate AED skills declined by 0.8% per month. A Kaplan-Meier analysis indicated that by 20 months about 40% of volunteers (in both arms) were no longer participating in the study, which corresponds to an attrition rate of about 2% per month.

Results of increased efforts to identify episodes at the sites were reported. The DSMB Chair noted that there had been a definite improvement. Reporting of net episodes increased from an average of 1.4 per 15 unit exposure months (UEMs) through May 14, 2002, to 2.5 episodes per 15 UEM for the period between May 14 and September 17, 2002. The rate for the entire duration of the study was 1.8 per 15 UEM, corresponding to a 29% increased in reporting of episode nets. Reporting of cardiac arrests followed a similar pattern though with a somewhat smaller net increase of 22%. The majority of sites demonstrated improved reporting. One site, Stony Brook, demonstrated a decrease in the number of episodes reported per 15 UEM.

Closed Session

The CTC described the data and assumptions for treatable cardiac arrests and for control group survival rates that were used in the power calculations. Implications associated with various study termination strategies were then discussed. Stopping data collection on September 30, 2003 would result in an unconditional power of about 76% for a 2-fold alternative. For a 2.1-fold alternative, power is about 82%. Adding a second interim monitoring of the data would result in roughly a 2% loss in power. Concern was expressed regarding the magnitude of the absolute difference required to obtain a 2-fold alternative with the observed survival of 16.5% in the control arm. The required survival in the intervention arm is now 33%.

Executive Session

The Board discussed importance of the PAD trial for public health, the reasonableness of the plan to extend follow-up, and the potential for type 2 errors that might occur if the trial were stopped on the previous schedule. The power curve is steep with changing estimates of the impact of defibrillators on survival from cardiac arrest, which also underlines the importance of continuing the trial.

Recommendations

The Board unanimously recommended that the trial be continued and that follow-up data collection should continue through September 30, 2003. The Board had no safety concerns.

The Board requested clarification of two episodes (patient ID's 20072 and 24088) where, at the family's request, no CPR was performed. The question was about the adequacy of the decision-making process leading to the withholding of CPR, and correspondences with good clinical practice and relevant state law. Ms. Powell reported that for the latter case, the patient was in an intermediate care facility where DNAR orders were not accepted. This patient did not want resuscitative measures performed. Responders began resuscitation until the family arrived with DNAR papers at which time the efforts were halted.

Action Item

- The CTC will provide the Board with documentation explaining the circumstances of the two cases mentioned above.

Next DSMB meeting: Tuesday, May 20, 2003, 11:00 a.m. Eastern (8:00 a.m. Pacific) was set for the next DSMB conference call.

The meeting ended at 12 p.m.

Costas T. Lambrew, M.D.
Chair

Yves Rosenberg, M.D.
Executive Secretary

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, MD 20892

MEMORANDUM

DATE:	December 12, 2002
FROM:	PAD Project Officer
SUBJECT:	Report of the November 13, 2002, PAD DSMB meeting
TO:	PAD Site Investigators

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Marcel E. Salive, MD, MPH
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